--83. The method of claim 81, wherein the cancer is of neuroectodermal origin.--

--84. The method of claim 83, wherein the cancer of neuroectodermal origin is a melanoma.--

--85. The method of claim 81, wherein the administering is effected at two or more sites.--

--86. The method of claim 85, wherein the administering is effected at three sites.

REMARKS

Claims 44-68 are pending in the subject application. With the amendments hereinabove, applicants canceled claims 44-68 without prejudice to applicants' right to pursue the subject matter of these claims in a divisional or continuation application. Applicants added new claims 69-86. Support for new claim 69 may be found inter alia on page 11, lines 13-20, page 32, lines 6-20, page 54, lines 12-14, page 65, lines 12-15, page 85, lines 9-14. Support for new claims 70-79 may be found inter alia from pages 11 to 14. Further support for new claim 79 may be found inter alia on page 43, lines 4-9 and page 53, line 35 to page 54, line 1. Support for claims 80-86 may be found inter alia on page 15, beginning line 27 to page 18, line 9. Accordingly there is no issue of new matter and applicants respectfully request the entry of this Amendment. Upon entry, claims 44-68 are under examination.

Double Patenting

The Examiner provisionally rejected claims 44-68 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claimed invention of copending Application

Nos. 08/477,097 and 08/475,784 for the reasons set forth in the last Office Action.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, applicants have hereinabove canceled claims 44-68 without prejudice and added new claims 69-86 in this subject application. For the pending applications, U.S. Serial Nos. 08/477,097 and 08/475,784, applicants have added new claims to obviate the raised double patenting rejection. For the Examiner's information, applicants have two more pending applications U.S. Serial Nos. 08/477,147 and 08/481,809 which has the same specification as this subject application, in which applicants have and will added new claims to obviate the double patenting rejection raised. Applicants believe that when the claims of these five applications are compared, there is no issue of double patenting.

§112 Rejection

The Examiner rejected claims 44-68 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed June 13, 1996.

The Examiner stated that applicants essentially argue the reference by Fung et al. should not be used to question whether antibodies against the ganglioside conjugate vaccines will prevent cancer since the experiments as set forth by Fung et al. were not used to study whether GM2-KLH conjugated vaccine prolonged survivability. The Examiner stated that applicants further argue there is no evidence by Fung et al. that the cancer cells express GM2, nor the antibodies to GM2 were generated after vaccination. The Examiner

stated that applicants arguments are not persuasive to obviate the rejection. The Examiner stated that whether or not the objective of Fung et al. experiments was to determine the efficacy of the GM2-KLH conjugated vaccine is not sufficient to overcome the rejection. The Examiner stated that as set forth previously, since the production of high titers of antibodies in melanoma patients with the GM2-KLH does not appear to correlate with the prevention of cancer as exemplified by the teachings of Fung et al., it is unpredictable if the composition as claimed is efficacious as a vaccine. The Examiner stated that beyond this, applicants arguments are not sufficient to obviate the rejection, since the art as exemplified by Cohen et al. (see Science 262:841-843 especially page 843) states: "Cancer vaccines are highly experimental." The Examiner stated that since the specification provides sufficient guidance of how to use the composition as a vaccine and the art at the time of the invention set forth cancer vaccines are highly experimental, it is reasonable to conclude a skilled artisan would be forced into undue experimentation to practice claimed invention.

The Examiner stated that applicants' amendment is sufficient to obviate the objection to the specification for the use of other gangliosides or chemically modified gangliosides. However, the Examiner stated that the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation, one skilled in the art is enabled to make derivatives of KLH. The Examiner stated that applicants arguments are not persuasive.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the Examiner stated that replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic

acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). The Examiner stated that Rudinger et al. teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstakingly experimental study." The Examiner stated that Salgaller et al. teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. The Examiner stated that Fox et al. teach methods for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these references demonstrate that an even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

In response, applicants respectfully traverse the above ground of rejection. Applicants have hereinabove canceled claims 44-68 without prejudice. New claims are directed to a composition comprising GM2 or GD2 ganglioside conjugated through the ceramide portion of the ganglioside to Keyhole Limpet Hemocyanin or a derivative thereof and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier and uses of said composition. Accordingly, new claims are

not directed to vaccine and thereby render the rejection to the vaccine claims moot.

Regarding the Examiner's statements about the derivatives of Keyhole Limpet Hemocyanin, applicants maintain that the specification have provided enabling teachings to generate such derivatives. See Specification page 12, lines 4-13. Applicants maintain that it will be routine experiments to generate said derivatives. Regarding the Examiner's specific comments about the variation of one or a few amino acids which may change the property of a protein, the disclosed specification has provided specific embodiments of Keyhole Limpet Hemocyanin being used as the immunogenic protein. The derivatives generated may easily be tested using the specific Keyhole Limpet Hemocyanin disclosed in the specification for comparison. Accordingly, there is no undue experimentation and applicants maintain that the derivatives of Keyhole Limpet Hemocyanin which can be used in the claimed invention have been fully enabled by the specification as filed.

In view of the foregoing discussion, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

§103 Rejections

Claims 44-46, 51-60 and 62-68

The Examiner rejected claims 44-46, 51-60, and 62-68 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) for the reasons set forth in the Office Action mailed June 13, 1996.

The Examiner stated that in response to applicants' piecemeal analysis of the references, one cannot show non-obviousness by

attacking references individually where, as here, the rejections are based on combinations of references. See MPEP 2145(d).

The Examiner stated that applicants assert that the cited references do not suggest or motivate one of ordinary skill in the art to make the claimed invention. The Examiner stated that applicants are not persuasive for the reasons as set forth in the last Office Action.

The Examiner stated that applicants appear to argue that the rejection should be withdrawn since from the prior art (e.g. Ritter et al.) does not suggest or provide an expectation that the oligosaccharide portion of ganglioside conjugate remains intact or needs to be intact. The Examiner stated that applicants arguments are not persuasive to obviate the rejection since applicants arguments are not commensurate in scope with the claimed invention. The Examiner stated that the claimed invention does not set forth that the oligosaccharide portion remains intact. The Examiner stated that beyond this while Rutter et al. (1991) may not characterize that the oligosaccharide portion remains intact with conjugation as asserted by applicants, it would have been reasonable to expect the conjugate of the prior art would have the same properties of the conjugate as claimed since conjugating the KLH to a ganglioside as set forth by Ritter et al. and as recited enhances the antibody response.

The Examiner stated that applicants argue that the rejection should be withdrawn since the prior art does not teach of the requirements (e.g. need) for an adjuvant. The Examiner stated that applicants argument is not persuasive since Livingston et al. set forth the vaccine administered to melanoma patient contains an adjuvant.

The Examiner stated that for the reasons set forth above in the

last Office Action, said rejection is maintained.

In response, applicants respectfully traverse the above ground of rejection. Applicants would like to point out the applicants have canceled claims 44-46, 51-60, and 62-68 without prejudice. New claims are directed to a composition comprising GM2 or GD2 ganglioside CONJUGATED THROUGH THE CERAMIDE PORTION of the ganglioside to a Keyhole Limpet Hemocyanin or a derivative thereof and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier and uses of said composition.

Applicants maintain the cited references, alone or in combination thereof do not disclose, teaches or suggest the conjugation of GM2 or GD2 through the ceramide portion of the ganglioside to an immunogenic protein. The cited references, alone or in combination thereof, do not provide any SPECIFIC teaching that the conjugation should be carried at the ceramide portion. In addition, applicants further maintain that the cited references do not disclose, teaches or suggest the composition comprising the above GM2 and GD2 conjugates and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree.

Accordingly, in view of the foregoing, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

Claim 61

The Examiner rejected claim 61 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) as applied to claims 44-46, 51-60, and 62-68 above and further in view of Kensil et al. and Marciani et al. for

reasons set forth in the Office Action mailed June 13, 1996.

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to the claims above. The Examiner stated that for the reasons set forth above, applicants arguments are not persuasive.

The Examiner stated that applicants assert that Kensil et al. and Marciani et al. do not suggest or motivate one of ordinary skill in the art to make the claimed invention. The Examiner stated that applicants arguments are not persuasive for the reasons as set forth in the last Office Action.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of the subject application, applicants have canceled claims 61 without prejudice, thereby rendering this ground of rejection moot. Independent claim 69 now recites the adjuvant which is a carbohydrate derviable from the bark of a Quillaja saponaria Molina tree, which is the subject matter of claim 61. Applicants believe that the Examiner's comments have been addressed by the response to the above ground of rejection.

Claims 47-50

The Examiner rejected claims 47-50 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) as applied to claims 44-46, 51-60, and 62-68 above and further in view of Irie et al. for the reasons set forth in the Office Action mailed June 13, 1996.

The Examiner stated that applicants appear to argue the rejection

should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims above. The Examiner stated that for the reasons set forth above, applicants arguments are not persuasive.

The Examiner stated that applicants argument that the teaching that GM2 is found on melanomas and breast carcinomas by Irie et al. does not provide sufficient motivation for one of ordinary skill in the art to practice the claimed invention is not persuasive. The Examiner stated that since Livingston et al. teaches of a vaccine for melanoma patients which stimulates the production of anti-GM2 antibodies and GM2 is associated with a variety of tumors (i.e. melanoma and breast) as taught by Irie et al., one of ordinary skill in the art would have been motivated to use the vaccine composition not only melanomas as set forth by Livingston, but also breast carcinomas since both types of tumors have GM2 present. The Examiner stated that for the reasons set forth above in the last Office Action, said rejection is maintained.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this subject application, applicants have hereinabove cancel claims 47-50 without prejudice. New claim 82 corresponds to the canceled claims 50 except that it ultimately depends on claim 69 recites a composition comprising a GM2 or GD2 ganglioside conjugated through the ceramide portion of the ganglioside to Keyhole Limpet Hemocyanin or a derivative thereof and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier. The additional citation of Irie et al. in combination with the previous cited reference does not render the composition obvious and therefore cannot render the dependent claim 82 obvious. Accordingly, applicants respectfully request the reconsideration and withdrawal of this ground of

rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the October 3, 1997 Office Action and earnestly solicit allowance of the claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the FOUR HUNDRED and SEVENTY-FIVE DOLLARS ($475.00) fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai Kit Chan

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents,
Washington, D.C. 20231.

Albert Wai-Kit Chan 4/2/98
Albert Wai-Kit Chan Date
Reg. No. 36,479

John P. White
Registration No. 28,678
Albert Wai-Kit Chan
Registration No. 36,479
Attorneys for Applicant(s)
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400